REMARKS

By this Amendment claim 1 has been amended to better define the invention, claim 3 has been canceled, claims 2 and 4-6 have been improved, and claims 24 and 25 revised. Entry is requested.

In the outstanding final Office Action the examiner has rejected claims 1, 2 and 4-6 under 35 U.S.C. 102(b) as being anticipated by Hiestand et al., he has rejected claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Hiestand et al. in view of Macauley, and he has rejected claims 24 and 25 under 35 U.S.C. 103(a) as being unpatentable over Hiestand et al.

The applicants assert that these rejections are without merit.

The present invention relates to the encapsulation of aphrons/ biliquid foam droplets in a polymer matrix to form a free flowing powder. This enables a controlled release system to be produced. The biliquid foam is very robust and enables the droplets to remain essentially intact within the polymer matrix powder. Release of the droplets may be achieved in numerous ways, for example see page 10, lines 16 to 30, "the rate of release of the entrapped biliquid foam may be controlled by the speed of dissolution when the powder makes contact with water or other polar liquid..." The use of hygroscopic polymer to form the powder enables the dissolution to release the droplets intact in a controlled manner

(hence the biliquid foam is resurrected from the powder intact, which is not possible with an emulsion and in particular with the prior art). Thus, the present invention provides a controlled release system in which it is not just oil that may be released from the powder but the biliquid foam droplets.

The robustness of the present invention is emphasized by the fact that the powders of the present invention may be formed into tablets in a tabletting process (see Example 12). A person of ordinary skill in the art knows that the compression process in generating tablets can cause loss of stability of droplets entrapped in the powder. However, the robustness of the entrapped biliquid foam droplets means that droplet size is maintained. Experimental evidence shows that the biliquid foam droplet size before spray drying and after release from the powder remains essentially the same. This would not be expected with an emulsion system and is a unique characteristic of biliquid foams. As outlined in Example 12 of the present application:

> "compression of the powder was performed using a tabletting machine. Successful tablets were produced. The powder was found to withstand high compression forces without affecting the redispersion of the oil droplets upon dissolution in deionized water and the droplet size distribution appeared unaffected."

Another feature of the powders of the present invention which results in the use of biliquid foams is that (see page 5, lines 16 to 19):

> "...it will be understood that the present invention enables oils to be incorporated into the powder which would normally be difficult to incorporate into conventional dry emulsion systems."

This is an important feature of biliquid foams as well as their robustness. An example of an oil which would be difficult to incorporate into an emulsion is found in example 11...Gransil GCM-5. Gransil GCM-5 is a silicone elastomer gel supplied by Grant Industries in USA.

As outlined in the Amendment filed July 7, 2008, emulsions are not the same as biliquid foams. Although they may be composed of hydrophilic phases, hydrophobic phases and surfactants, their structure is not the same. Emulsions are typically oil droplets suspending in an aqueous medium. The droplet may be surrounded by a single layer of surfactant molecules to prevent coalescence with neighboring droplets. Each phase is stabilized relative to each other phase by a single layer of surfactant molecules. If emulsions are diluted, the different phases will no longer be stable, and coalesce into two separate phases, a water and an oil phase. In contrast to this, a biliquid foam may be diluted by the addition of more external phase, or continuous phase without the addition of more surfactant without coalescing into two separate phases. The

examiner has stated that the features, i.e., the double layers of surfactants, and the properties of polyaphrons are not recited in the claims and cannot therefore be relied upon to distinguish the present invention from that of the prior art. It is submitted that the examiner is mistaken in this regard. A person of ordinary skill in this art knows that biliquid foams have the properties described, and that these properties distinguish biliquid foams from emulsions. Just because these differences are not specifically recited in the claims does not mean that they are not inherent in the properties of biliquid foams.

The examiner is referred to Sebba, U.S. Patent No. 4,486,333. Professor Felix Sebba of Virginia State University was well known for his work in the field of biliquid foams. This patent is also referenced in the specification of the present application. Oil-in-water emulsions are distinguished from biliquid foams (polyaphron dispersions) in this document. In particular, the examiner is referred to column 1, lines 31 to 46:

> "The water-lamella biliquid foams with which the present invention is concerned are to be distinguished from oil-in water emulsions in which the discontinuous oil phase is separated from the continuous aqueous phase by a single interface. In the composition under consideration, the globules of non-polar liquid are encapsulated in a double surfaced film of hydrogen bonded liquid which is immiscible with the non-polar liquid and contains a soluble surfactant."

In column 5, lines 61 to 65, Sebba states that:

"The polyaphrons are characterized by extremely small non-coalescing globules of non-polar liquid. This is because of the encapsulating surfactant film which surrounds each globule and acts as a barrier to coalescence, thus clearly distinguishing the system from an emulsion."

An annex which further describes biliquid foam is attached.

Macaulay

Macaulay discloses a process for making a substantially dry free-flowing powder of microscopic discrete capsules. The capsules possess a shell or wall containing a marking fluid (col. 1, lines 20 to 20 and as shown in Figure 1). The process of making the capsules of Macaulay involves first making an emulsion. The continuous phase of the emulsion is formed of a film-forming material (see column 4, lines 35 to 53). The discontinuous phase constitutes a marking fluid which comprises a pigment, or colored dye. The shell or wall of the capsule is formed from the continuous phase of the emulsion. Thus, when the capsule of Macaulay has been formed it comprises a shell formed of a film-forming polymer (11, see Figure 1) encapsulating the marking fluid (10, see Figure 1). There is no disclosure of a capsule or powder encapsulating an emulsion in Macaulay. This differs from the present invention. In the present invention biliquid foam droplets are encapsulated within a

polymer matrix and not inextricably tied to the dry powder. Thus, when release occurs, the biliquid foam reverts to its original structure. Release from the Macaulay capsules is by rupture alone as the shell of the capsule breaks under pressure and the marking fluid is released. No emulsion is released.

Hiestand et al.

Hiestand et al. disclose a process for encapsulating a hydrophobic liquid in aqueous emulsion with a wall-forming polymeric material by causing a coacervate solution of the wall-forming polymeric material to deposit about the hydrophobic liquid in aqueous emulsion (see the abstract). In particular, Hiestand et al. disclose a process for encapsulation of an emulsion with a wall forming polymeric material. The capsule is formed by a wet process as a coacervate solution is hardened to form a capsule wall. The treated coacervate is then separated by centrifuging, filtering, decanting or the like. Then the capsules are dried by spray drying, freeze drying etc. This is a multi staged complex process. In contrast, the current invention takes a mixture of the biliquid foam and the polymer, spray dries, freeze dries or granulates to form the biliquid foam entrapped in the polymer as a free flowing powder. Thus, the process is much simpler and the droplets still exist as discrete biliquid foam system, unlike Hiestand et al. where the coacervate changes the emulsion forever. The release from Hiestand et al. is through the wall of

the capsule as sustained or controlled release. This is possible with the present invention also, but in addition the rupture mechanism and the release by chemical or physical dissolution of the polymer matrix to reveal the intact biliquid foam is also possible. The Hiestand et al. system is very limited in polymer chemistry choice (a hardening process is required), functionality of the wall (no water soluble systems) and the process requires specialist chemistry for the coacervation.

There is no disclosure in Hiestand et al. of claim 1:

> "A discrete powder which comprises particles of a matrix of a polymeric material encapsulating droplets of biliquid foam, wherein the biliquid foam has a continuous and an oil phase and the biliquid foam droplets encapsulated in the polymeric material have a mean droplet size in the range of from 1 to 45 μm, and the powder has a mean particle size in the range of from 5 to 150μm."

In particular, Hiestand et al. is silent on biliquid foams. (As outlined above, they are not the same as emulsions, as evidenced by Sebba). Hiestand et al. is silent on the size of the droplets of the biliquid foams encapsulating the polymer. Moreover, Hiestand et al. is silent on the powder having a mean particle size in the range of from 5 to 150 μm, as acknowledged by the examiner.

It is therefore submitted that amended claim 1 is not anticipated by Hiestand et al. It is further submitted that the present invention is not obvious over Hiestand et al. and Macaulay.

The examiner notes that Hiestand et al. state that the size of the particles (e.g., emulsion capsules) are taught to be dependent in part, on the degree of dispersion or size of the emulsion droplets in the primary emulsion. In addition, the capsule size is a function of the thickness of the coacervate coating (column 6, lines 43 to 54). Hiestand et al. is silent on the specific range of particles size and the specific mean droplet size of the biliquid foam.

As outlined above, the differences between the present invention and that of Hiestand et al. are three-fold:

(i) The present invention uses biliquid foams, not emulsions;

(ii) Hiestand et al. is silent on the size of the droplets encapsulated in the polymer; and

(iii) Hiestand et al. is silent on the powder having a mean particle size in the range of from 5 to 150μm.

The combination of all three of these differences leads to a powder which has significantly improved properties for use as a controlled release system. The powders of the present invention have the unexpected advantage that even after the powder has been compressed into a tablet, and the oil droplets are subsequently released from the powder by

dissolution of the polymer, the oil droplets size distribution is substantially unaffected (see Example 12).

Biliquid foams are very robust. Typically, compression processes used in generating tablets leads to a loss in the stability of droplets entrapped in a powder. However, the present inventors have surprisingly found that the stability of the entrapped biliquid foam enables the droplet size to be maintained during spray drying and in the discrete powder itself. The powder of the present invention may be compressed to form a tablet and even after compression, upon dissolution of the tablet in, for example deionized water, the droplet size of the released biliquid foam remains unaffected (see page 32). This would not be expected with oil-in-water emulsions described in Hiestand et al., and is thought to be a unique characteristic of biliquid foams. This property allows the droplet size of the biliquid foam to remain essentially the same after entrapment and release, and is particularly important when the discrete powder is used, for example, in drug delivery systems (see page 5, lines 20 to 23).

Thus, unlike the prior art powders, even after dissolution of the polymer, the structure and size of the biliquid foam is maintained. Having biliquid foam droplets in the range of from 1 to 45 μm means that there is a high surface to volume ratio which is useful for example for delivery of an active. The size of the droplet is the same after encapsulation in the polymer, and subsequently after release from the powder. This is

important in many applications for controlled release of an active, none more so than in pharmaceutical products, such as tablets, where the system must be reproducible and predictable time after time and after storage. This is of particular use in, for example, drug delivery systems. This is evidenced in Example 12 of the application. The attached PowerPoint slides also show details of the powder comprising the biliquid foam. Experimental evidence shows that the biliquid foam droplet size before spray drying and after release from the powder remains essentially the same. This would not be expected with an emulsion system and is a unique characteristic of biliquid foams.

Thus, the invention is far more flexible than Hiestand et al. and Macauley. It would not be obvious to one skilled in the art to make a leap from these rigid capsule systems to the new invention. The release of Macaulay is through rupture only. The release from the Hiestand et al. is through the wall of the capsule. The release with the present invention may be either of these two mechanisms. However, additionally the release may be through chemical (e.g., degradation) and/or physical (e.g., dissolution) of the polymer releasing the intact biliquid foam. Even after release the structure and size of the biliquid foam is maintained.

The examiner refers to Macaulay and specifically to column 3, line 73 to column 4, line 17 where Macaulay states that the resulting powder capsules desirably are between about 0.1 and 70 microns in diameter.

More desirably, the diameters of the capsules is from 0.5 to 20 microns. This document goes on to teach that it is desirable to employ microscopic capsules in pressure-sensitive copying systems which do not require the use of excessive pressures, so capsules having a diameter of from 1 to 5 microns are preferred. The examiner states that in the light of these documents the skilled person would routinely optimize the particle size to arrive at the present invention. It is however submitted that the examiner is mistaken in this regard.

The particle diameters referred to in Macaulay relate to oils encapsulated in a polymer shell, not to a powder which encapsulates an emulsion or a biliquid foam. In Macaulay the system is designed so that when the polymer system is burst the oil (marking fluid) is released dying the material. Thus, the whole design of particle size of Macaulay is based on the fact that upon rupture of the powder the whole system is broken down into its primary constituents (oil and the polymer shell). In contrast to this, upon rupture or dissolution of the polymer in the present invention, the system is designed not to release oil and the continuous phase of the biliquid foam as discrete and separate phases. Instead, biliquid phase droplets are released. In the system of Hiestand et al. if the coacervated polymer is burst, as emulsions are not stable upon dilution, the constituent oil and continuous phases of the emulsion separate, i.e., it is not possible to obtain the stable emulsion by rupture of

the polymer. Moreover, in Hiestand et al., the chemical make-up of the original emulsion is altered by the coacervation process, thus the substance released will differ from the original emulsion. As outlined above, it is advantageous, particularly when the biliquid foams comprise active agents such as pharmaceuticals for the size of the biliquid foam to be known after dissolution/rupture of the powder. This is important, for example, if an active agent is to be transported through a membrane or skin. Such control is not possible in prior art methods.

In view of the above it would not be obvious for the person of ordinary skill in this art, desiring to provide an improved controlled release system, to arrive at the present invention.

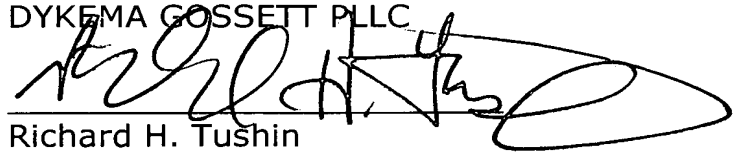
The examiner suggests that claims 24 and 25 are not patentable. In particular, the examiner states that while the specification is enabled for "one or more pharmaceuticals," such as ibuprofen, this application does not reasonably provide enablement for the broader incorporation of "contains pharmaceuticals." The examiner is of the view that the present application provides support for the incorporation of only <u>one</u> drug into the composition. Notwithstanding the fact that the applicants disagree with this observation, in order to expedite the prosecution of the application, claims 24 and 25 have been amended to reference a single pharmaceutical.

It is further submitted that subject matter of claims 24 and 25 are inventive over Hiestand et al. Hiestand et al. teach that the products described provide an improved provision of impermeable coatings of high strength or coatings which permit the gradual release of contents for water-soluble materials (see column 3, lines 36 to 40). The incorporation of pharmaceuticals into the products of Hiestand et al. are only disclosed only for use in sustained release forms (see column 3, lines 54 to 61). There is no suggestion in Hiestand et al. of incorporating a pharmaceutical into the oil phase of powder. It would, therefore, not be obvious to arrive at the subject matter of claims 24 and 25 in the light of the prior art.

Favorable reconsideration is requested.

Respectfully submitted,

DYKEMA GOSSETT PLLC

By: 

Richard H. Tushin
Registration No. 27,297
Franklin Square, Third Floor West
1300 I Street, N.W.
Washington, DC 20005-3353
(202) 906-8680

ANNEX 1
BILIQUID FOAMS

By biliquid foam as used herein is meant a particular kind of hydrophobic liquid-in-hydrophilic liquid dispersion comprising (a) a hydrophilic liquid miscible phase, (b) a second hydrophobic phase being immiscible or substantially immiscible with the first phase and (c) one or more surfactants, wherein the dispersed or discontinuous phase is in the form of small (e.g. 1 to 45 micron diameter) droplets, and the whole having the following characteristics, which distinguish biliquid foams from conventional or common emulsions and other dispersion types:

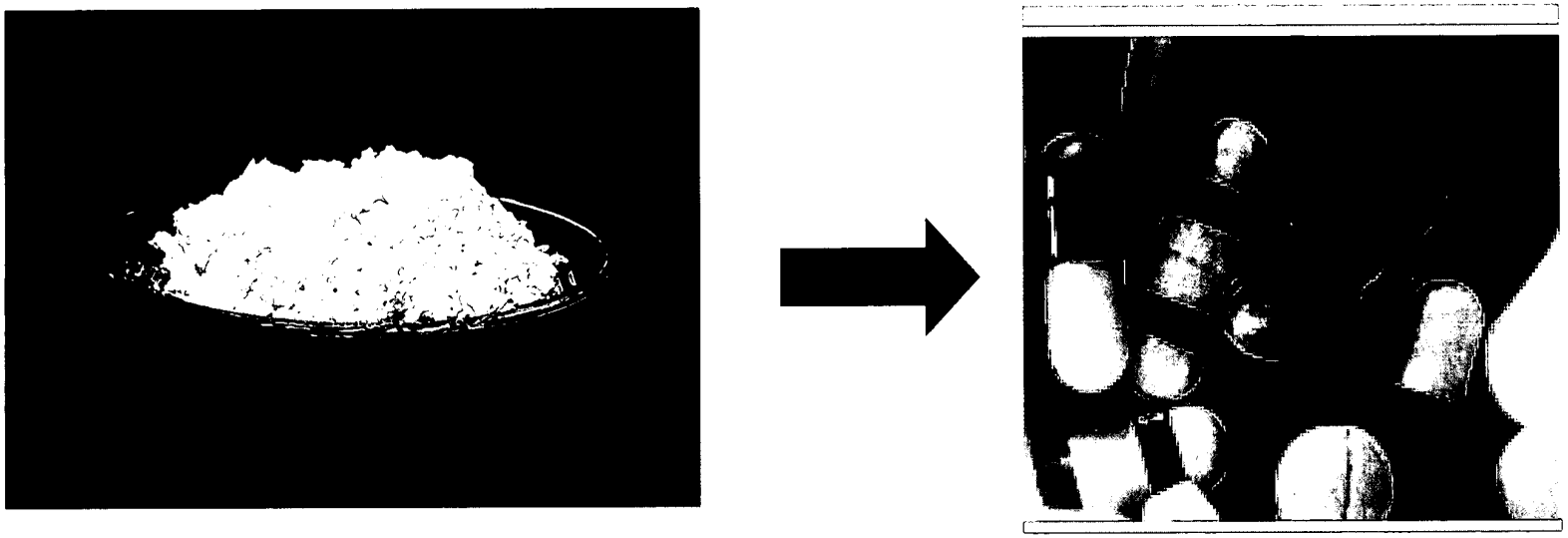
1. They are capable of existing in a stable form wherein the volume fraction of the dispersed phase (ϕ_{ip}) is greater than 0.7 and can be as high as 0.97. (ϕ_{ip} is the volume ratio of discontinuous to continuous phase expressed as a fraction).
2. The microscopic appearance of biliquid foams where ϕ_{ip} is greater than 0.7 is that of an aggregate of individual droplets, pushed closely together into polyhedral shapes, resembling the appearance of a gas foam. In this form, the dispersion has gel-like properties and is referred to as a Gel Polyaphron Dispersion (GPD).
3. Stable biliquid foams can be formed with a surfactant concentration less than 3% and more typically less than 2% by weight of the total composition.
4. Gel Polyaphron Dispersions (as described in 2 above) can be diluted to any extent by the addition of more continuous phase without the addition of more surfactant, when the gel-like properties disappear. Once ϕ_{ip} has been reduced to below 0.7, the individual droplets of internal phase become separated to take the form of spherical droplets, which remain stable and intact but which may nevertheless join together in loose associations and float to the top or sink to the bottom of the diluted dispersion (depending on the relative densities of the two phases). In this diluted form each droplet is referred to as a Colloidal Liquid Aphron (CLA). Simple shaking of the diluted dispersion instantly causes a homogeneous, stable dispersion of Colloidal Liquid Aphrons to re-form.

Each of the above characteristics and a combination of them clearly differentiate the biliquid foams of the present invention from conventional emulsions and other dispersion types which do not have all of those characteristics. Biliquid foams are disclosed in the following literature references by Sebba: "Biliquid Foams", J. Colloid and Interface Science, 40 (1972) 468-474 and "The Behaviour of Minute Oil Droplets Encapsulated in a Water Film", Colloid Polymer Sciences, 257 (1979) 392-396, Hicks "Investigating the Generation, Characterisation, and Structure of Biliquid Foams", PhD Thesis, University of Bristol, 2005, Crutchley "The Encapsulation of Oils and Oil Soluble Substances Within Polymer Films", PhD Thesis, The University of Leeds, 2006 and Lye and Stuckey, Colloid and Surfaces, 131 (1998) 119-136. Biliquid foams are also disclosed in US-A-4,486,333 and WO 97/32559.

Spray Dried Dispersions (SDD)

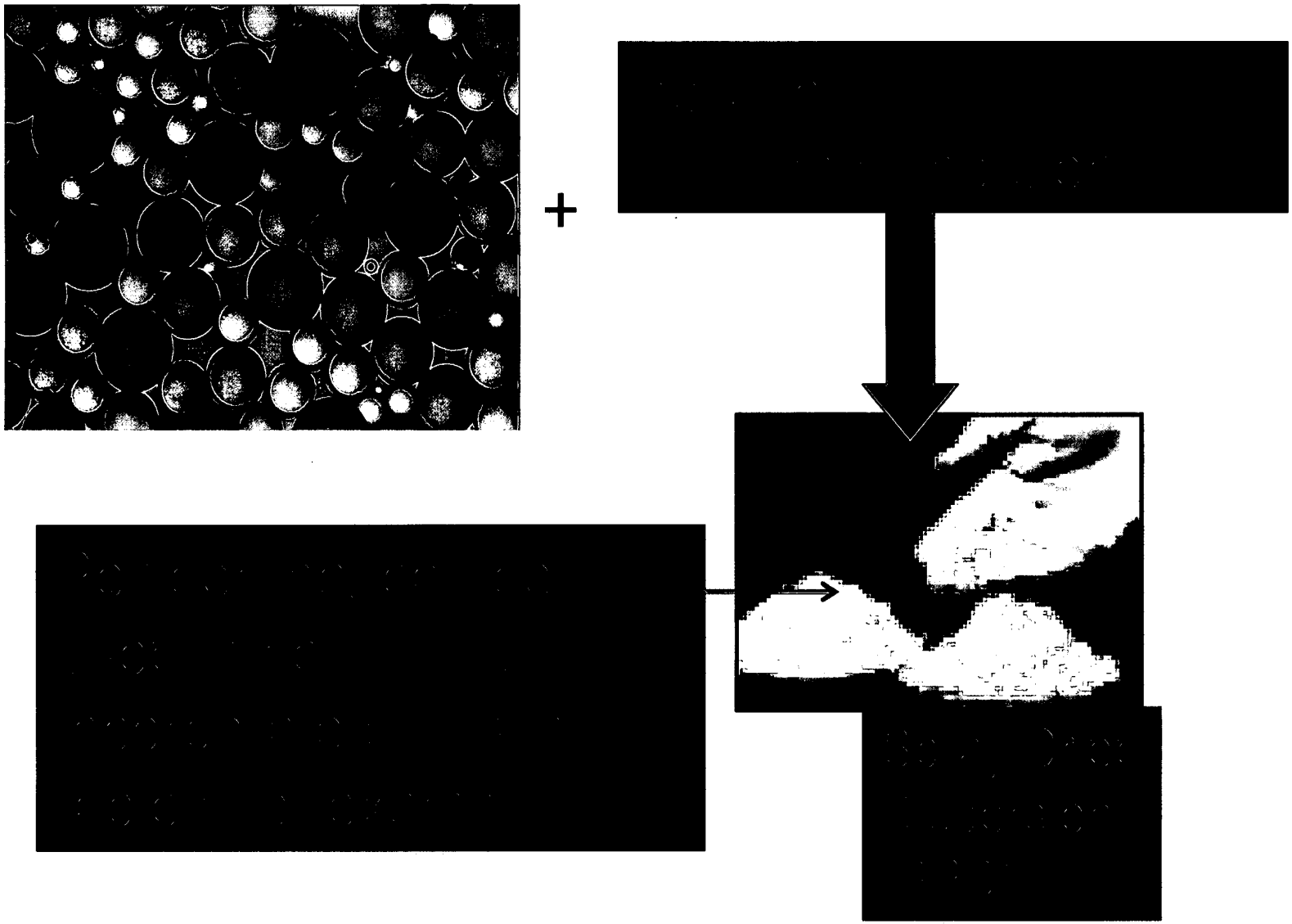
Spray Dried Dispersions

Can be pressed into tables or filled into capsules

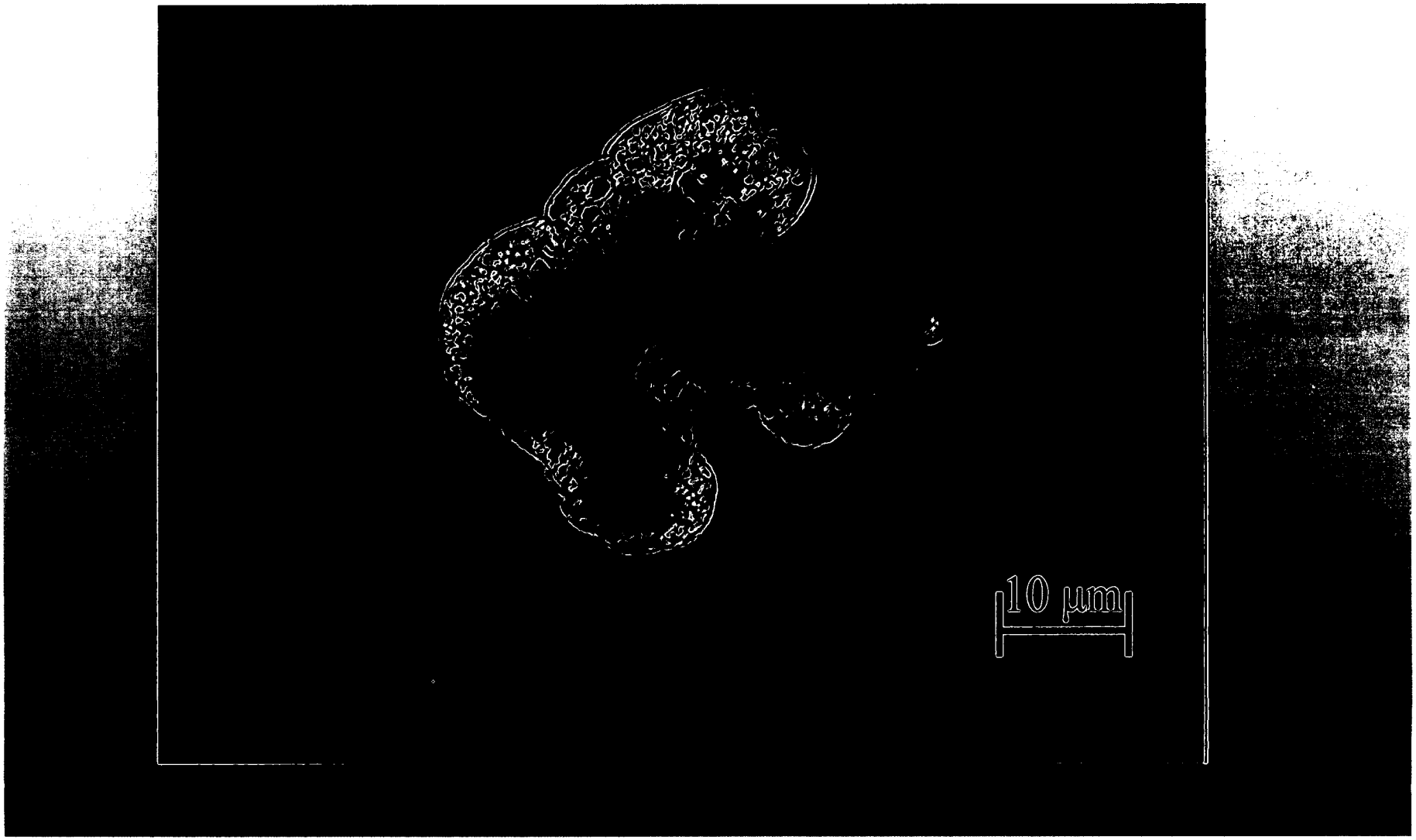


Oil soluble drugs are released as a highly dispersed liquid solution

Spray-Dried Dispersions (SDD)



Spray Dried Powder Particle
(Magnification X400)



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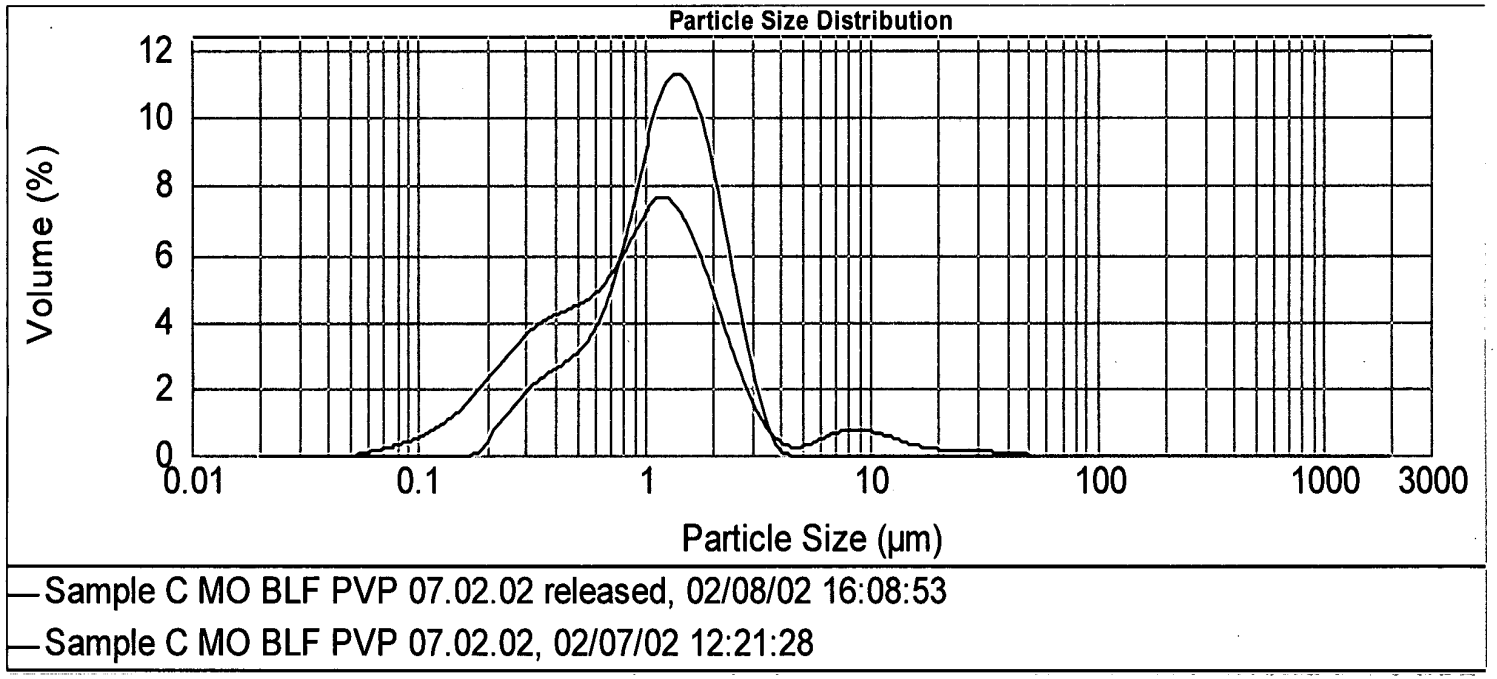
Spray Dried Powder Particle
(Magnification X400)

Spray Dried Powder – Preservation of Biliquid Foam/Aphron Size Distribution



The size distributions of the biliquid foam before spray drying (green) and after release from the table or powder (red) are virtually identical.

Spray Dried Powder – Oil Soluble Drug Loading Capacity

Solubility of drug %	% of drug in tablet	Mg of drug per g of tablet
5	1.8	18
10	3.6	36
20	7.2	72
30	10.8	108
40	14.4	144
50	18.0	180